

Stereoselective Synthesis of α,α' -Dihydroxy- β,β' -diaryl- β -amino Acids by Mannich-like Condensation of Hydroarylamides

Ilir Pecnikaj,^[a] Francesca Foschi,^[a] Raffaella Bucci,^[b] Maria Luisa Gelmi,^{*,[b]} Carlo Castellano,^[a] Fiorella Meneghetti,^[b] and Michele Penso^[c]

[a] Ilir Pecnikaj, Francesca Foschi, Carlo Castellano

Department of Chemistry, University of Milan, via Golgi 19, I-20133 Milano, Italy

ilirpp@yahoo.it, francesca.foschi@uninsubria.it, Carlo.Castellano@unimi.it

[b] Raffaella Bucci, Maria Luisa Gelmi, Fiorella Meneghetti Department of Pharmaceutical Sciences (DISFARM), University of Milan, via Venezian 21, I-20133 Milano, Italy

raffaella.bucci@unimi.it, marialuisa.gelmi@unimi.it, fiorella.meneghetti@unimi.it

[c] Michele Penso, CNR–Institute of Molecular Science and Technologies (ISTM), via Golgi 19, I-20133 Milano, Italy

Michele.Penso@istm.cnr.it

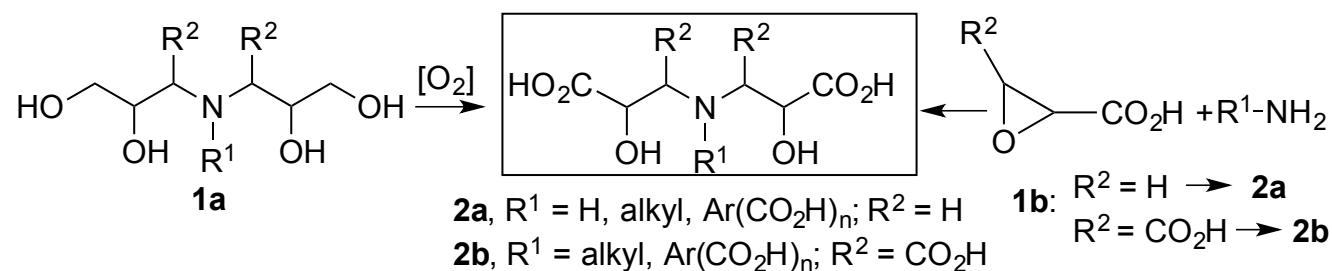
Abstract: *Dual* α,α' -Dihydroxy- β -amino acids are very interesting tools for several industrial applications. Nevertheless, few derivatives are reported in the literature concerning the substitution pattern as well as their enantioselective syntheses are lacking. Here, we report on the preparation of enantiopure α,α' -dihydroxy- β,β' -diaryl- β -amino acid (*dual*) derivatives by an efficient Mannich-like condensation of hydroarylamides with 5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one (triethylsilyl)ketene acetal. The synthetic protocol has been optimized affording the *dual* compounds in very good yields and with different aryl substitution patterns. Taking advantage of the “double stereodifferentiation” concept,

a highly stereoselective reaction was performed: of the 16 possible isomers, only two diastereoisomers (*d.r.* up to 93:7) formed. Insights on the high stereocontrol of this condensation were given.

Introduction

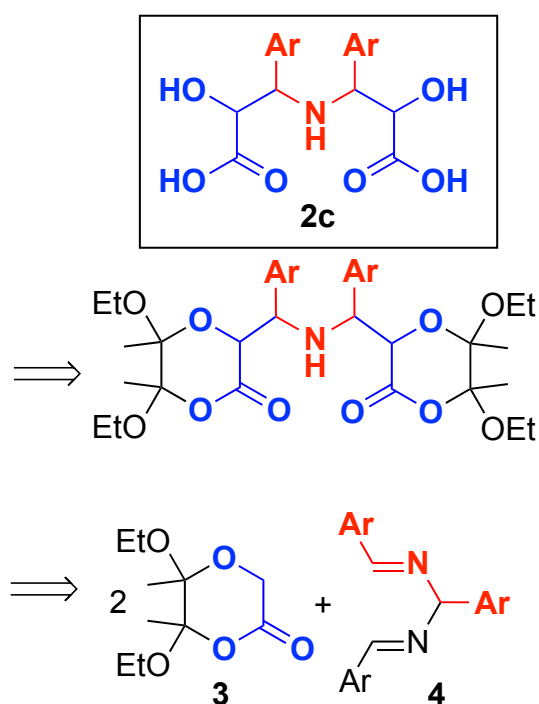
Over the last two decades, there has been increasing interest in the chemistry of β -amino acid derivatives since these non-proteinogenic molecules have been extensively used to build new bioactive poly-functionalized molecules,^[1] peptidomimetics and foldamers^[2] and materials.^[3] Focusing on α -hydroxy- β -amino acids, they are particularly profitable as pharmaceutical compounds.^[4] As documented by several patents, the parent *dual* α -hydroxy- β -amino acid derivatives **2** (Scheme 1) have found industrial application as chelating agents in detergents,^[5] bleaching processes for photography,^[6] electrostratographic toner preparation,^[7] biological treatment of waste water,^[8] to prevent corrosion processes, and in formulations for skin care products^[9] and biocides.^[10] On the other hand, *dual* amino acids could be very appealing for the preparation of peptidomimetic with exotic architectures.

Nevertheless, only few racemic *duals* **2** are described in the literature. In the known structures, both $C_\beta/C_{\beta'}$ are unsubstituted (**2a**) or bear an additional carboxylic function (**2b**). The simplest *duals* **2a** have been prepared via tertiary *N,N*-bis(2,3-dihydroxy-propyl)amines **1a**, through O_2 oxidation of the hydroxy-methylene groups,^[11] or by amine nucleophilic ring-opening of glycidic acid derivatives **1b** ($R^2 = H$). This protocol applied to the oxirane-2,3-dicarboxylic acid produces the more polar compounds **2b** ($R^2 = CO_2H$).^[12] It is to be point out that the above compounds are produced in racemic form and diastereisomeric mixture.



Scheme 1. *Dual* α -hydroxy- β -amino acids **2a,b** from literature.

The paucity of the substitution pattern in the known *dual* α -hydroxy- β -amino acids **2a,b** and the large number of applications of these structurally simple derivatives, focused our ongoing studies on exotic β -amino acids^[13] toward the synthesis of new chiral β,β' -diaryl *duals* **2c** (Scheme 2), adopting an original challenging strategy in term of protocol and stereochemistry control. To include the glycolic acid moiety into the target structure, two molecules of the lactone **3** were condensed in the presence of InCl_3 with a molecule of *N,N'*-diarylidene-1-arylmethanediamine (or hydroarylamide) **4**.



Scheme 2. Retrosynthetic scheme for the synthesis of *dual* α -hydroxy- β -amino acids **2c**.

The InCl_3 promoted Mannich-like reaction was optimized, mostly in term of reagents ratio. Different hydroarylamides **4** were tested making this procedure general for the preparation of *dual* compounds **2c**. Even if four stereocenters were generated during the condensation process, by using the enantiopure lactone a highly stereoselective control was achieved. Actually, of the 16 possible isomers, only two diastereoisomers were formed, being one of them the largely major product (*d.r.* up to 93:7). Studies

performed to rationalize this behavior indicated, most probably, that a double stereodifferentiation drives these excellent stereochemical results.

Results and Discussion

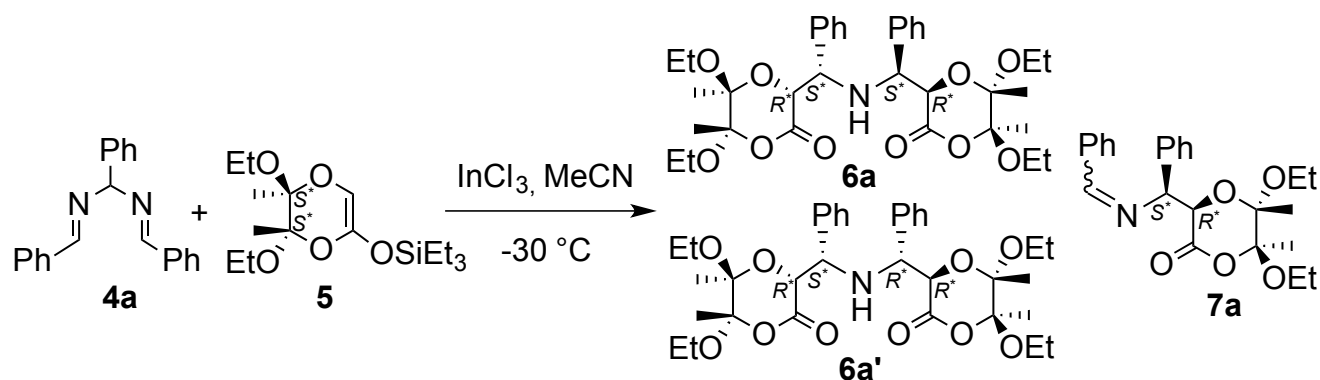
To access natural and unnatural isoserines, several smart synthetic methods have been developed.^[14] Recently, we described the use of acid catalyzed Mannich-like condensation reactions of imines and the racemic “Ley’s lactone”^[15] analogous (triethylsilyl)ketene acetal **5**, for the diastereoselective synthesis of α -hydroxy- β -amino acid derivatives^{13c} and 3-substituted morpholine-2-carboxylic esters.^[13d]

Here, we apply the above strategy to the synthesis of *dual* compounds **2c**, using hydroarylamides **4**^[16] as imine counterpart. Initially, this condensation was studied (Table 1) by adding InCl₃ to a solution of racemic TES-acetal **5** and hydrobenzamide (**4a**) (*Method A*).

In the reaction between equimolar amount of **4a** and **5** with sub-stoichiometric InCl₃ (entry 1), *dual* **6a/6a'** mixture and imine **7a** were the most abundant components of the crude, together with benzaldehyde and lactone **3** as byproducts. With an excess of hydrobenzamide (entry 2), only **7a** was obtained in good yield. With a reversed **4a/5** molar ratio (entry 3), a substantial increase of both **5** conversion (84%) and *duals* yield (42%) was reached. The reaction did not proceed with InCl₃ 10% molar, whereas by increasing it to 1 molar equivalent (entry 4) *duals* were the major products. When excess of both **5** and InCl₃ (entry 5) was used, a large quantity of lactone **3** formed together with the target compounds **6**.

The reaction is strongly dependent on the addition order of reagents, as proved by the dramatic effect found when TES-acetal **5** was added at -30 °C to a solution of hydrobenzamide/InCl₃ (*Method B*): in all cases, starting materials were rapidly consumed (entries 6–8). Condensations carried out using excess of either **5** (entry 6) or **4a** (entry 7) gave similar results, the imine **7a** being the major product (58–63%). The goal in obtaining **6a/6a'** in good yields (62%) was reached by operating with a large excess of both TES-acetal **5** and InCl₃ (entry 8).

Table 1. Screening of the reaction conditions for the reaction of racemic **5** with hydrobenzamide **4a**.^[a]

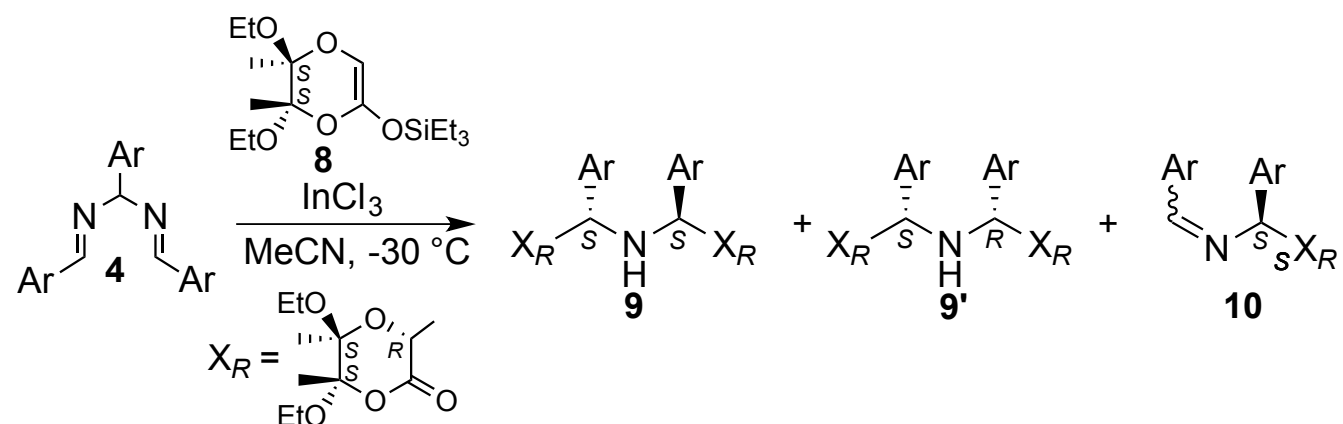


entry	4a : 5 :InCl ₃ ^[b]	method ^[c]	<i>t</i> (min) ^[d]	6a (%)	6a' (%)	7a (%)
1	1:1:0.5	A	90	25	11	16
2	1:0.5:0.25	A	30	6 ^[e]	7 ^[e]	59 ^[e]
3	1:2:0.5	A	90	35	7	42
4	1:2:1	A ^[f]	30	50	6	15
5	1:2:2	A	90	45	13	16
6	1:2:1	B	10	18	7	63
7	1:0.5:0.5	B	10	7 ^[e]	—	58 ^[e]
8	1:3:2	B	10	60	2	18

[a] In all the reactions, solutions (1 mol L⁻¹) of **4a**, **5** and InCl₃ in MeCN were used. [b] Molar equivalent ratio. [c] *Method A*: the hydrobenzamide (**4a**) and TES-acetal **5** solutions were mixed at 25 °C; this mixture cooled at -30 °C was stirred for 10 min, then the InCl₃ solution was added. *Method B*: InCl₃ and **4a** solutions were mixed at 25 °C and the resulting mixture was stirred at -30 °C until some solid crystallized (1 h). The TES-acetal **5** solution was then added and the mixture was stirred at -30 °C for further 10 min. [d] Time from the addition of the last reagent (*Method A*: InCl₃; *Method B*: TES-acetal **5**). [e] Referred to **5**. [f] The reaction carried out under the conditions of entry 4, but at 25 °C, gave only decomposition products.

The generality of the above procedure was proved by applying the more efficient conditions (*Method B*) to a series of hydroarylamides **4** and using a masked enantiopure glycolic acid derivative (Table 2).

Table 2. Stereoselective condensation of hydroarylamides **4** with enantiopure (5*S*,6*S*)-TES-acetal **8**.^[a]



	4	Ar	<i>duals</i> (%)		<i>imine</i> (%)
1	4a ^[b]	Ph	9a (63)	9a' (5)	10a (18)
2	4a ^[b,c]	Ph	ent-9a (62)	ent-9a' (5)	ent-10a (18)
3	4b ^[b]	4-MeC ₆ H ₄	9b (51)	9b' (8)	10b (24)
4	4c ^[b]	4-MeOC ₆ H ₄	9c (47)	9c' (6)	10c (25)
5	4d ^[b]	4-FC ₆ H ₄	9d (43)	9d' (7)	10d (50)
6	4d ^[c]	4-FC ₆ H ₄	ent-9d (43)	ent-9d' (6)	ent-10d (48)
7	4e ^[b]	4-BrC ₆ H ₄	9e (60)	9e' (8)	10e (26)
8	4a ^[d]	Ph	9a (20)	9a' (9)	10a (66)
9	4b ^[d]	4-MeC ₆ H ₄	9b (23)	9b' (3)	10b (68)
10	4c ^[d]	4-MeOC ₆ H ₄	9c (25)	—	10c (65)
11	4d ^[d]	4-FC ₆ H ₄	9d (18)	9d' (2)	10d (75)
12	4d ^[c,d]	4-FC ₆ H ₄	ent-9d (19)	—	ent-10d (72)
13	4e ^[d]	4-BrC ₆ H ₄	9e (28)	9e' (3)	10e (60)

[a] *Method B* was applied, using solutions (1 mol L⁻¹) of **4**, **8** and InCl₃ in MeCN. [b] **4**:**8**:InCl₃, 1:3:2 molar ratio. [c] In the condensation, (5*R*,6*R*)-(triethylsilyl)ketene acetal **11** was used instead of **8**. [d] **4**:**8**:InCl₃, 1:2:1 molar ratio.

Even if the synthesis of the 5,6-dimethoxy Ley's lactone derived (5*S*,6*S*)-(triethylsilyl)ketene acetal was reported in the literature,^[15b] we decided to prepare and use the new chiral 5,6-diethoxy parent **8**, that we expected to be more effective in the Mannich condensation diastereoselectivity control, analogously to the racemic acetal **5**. The synthesis and the tricks to obtain **8** in very good yields, operating in batch conditions, are reported in the Supporting Information (Scheme S1).

The reaction between **4** and **8** was performed by modulating the reagents molar ratio in order to control the inherent selectivity of the reaction.

High conversions (78–94%) of **4** and good yields (50–68%) of enantiopure *duals* **9/9'** were reached by using the **4:8:InCl₃** molar ratio 1:3:2 (entries 1, 3-5, 7). Both electron-donating (entries 3,4) and electron-withdrawing substituents (entries 5,7) were tolerated on the hydroarylamide moiety. Together with *dual* compounds, relevant amounts of imines **10** (18–50%) were isolated. In all cases, *dual* **9** was prevalent over the diastereoisomer **9'** (*d.r.* up to 93:7), demonstrating the high diastereoselectivity of this Mannich-like condensation. As expected, when (5*R*,6*R*)-(triethylsilyl)ketene acetal **11** was used instead of **8**, a similar products distribution was found, the enantiomeric *dual* **ent-9** being the major product (entries 2, 6).

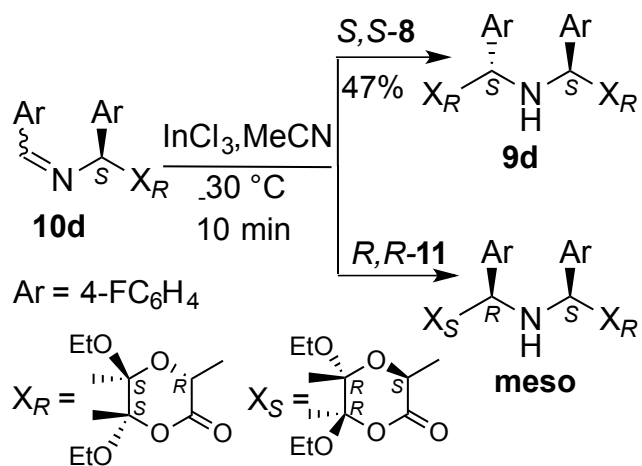
The above protocol was applied to hydroarylamides derived from the more sterically demanding 1-naphthaldehyde and from salicylaldehyde. The reaction fails in the first case and in the second one gave only by-products, probably due to the presence of the acid phenolic group.

Finally, by changing the molar ratio (**4:8:InCl₃**, 1:2:1, entries 8-13), imines **10** were isolated as major product (60–75%), accompanied by minor amounts of **9** (18-28%) and **9'** (2-9%).

In conclusion, by using *Method B*, it is possible to tune the formation of dual compounds **9/9'** or imines **10**, valuable tools for other condensation reactions, simply by changing the molar ratio between the reagents.

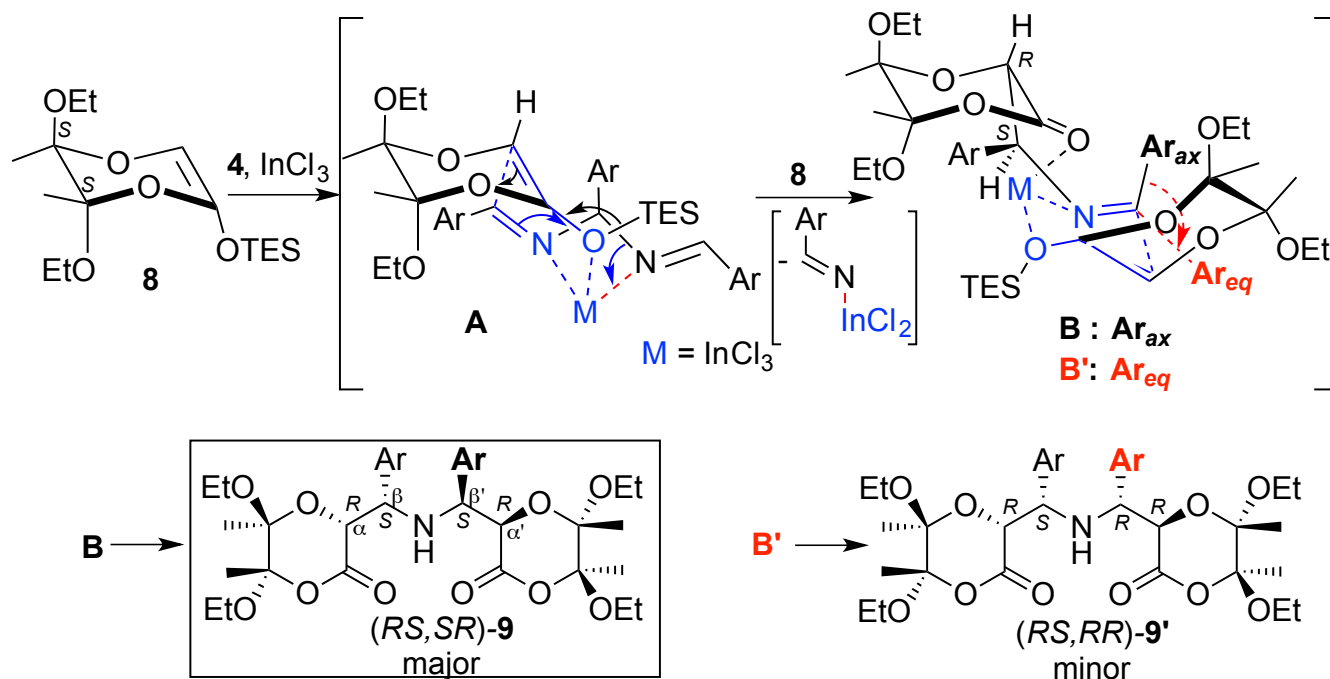
To verify whether imines **10** was an intermediate in the *duals* construction and to rationalize the stereochemical result of the above reaction, **10d** was made to react with both (5*S*,6*S*)-(triethylsilyl)ketene acetal **8** and its enantiomer (5*R*,6*R*)-(triethylsilyl)ketene acetal **11** (Scheme 3). In the first case, the diastereoisomer **9d** was isolated as the sole condensation product. On the other hand, **10d** did not react with **11** to form the *meso* diastereoisomer (Scheme 3). This behavior shows that the second condensation was strongly dependent on the stereochemistry of the nucleophile, and that a significant mismatch was operative between **10d** and **11**.

This reaction demonstrates that the imine **10**, far from being only a condensation by-product, can be a useful intermediate for the preparation of both *duals* and other non-symmetric double Mannich-like condensation products.



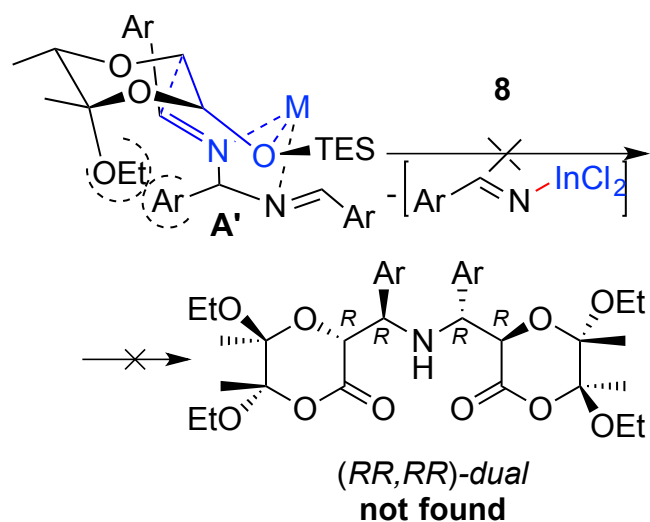
Scheme 3. Match and mismatch in the condensation of imine **10d** with TES-acetals *S,S*-**8** and *R,R*-**11**.

To rationalize the stereoselectivity of this reaction, we propose a mechanism (Scheme 4) that takes into account the transition state assumed for analogous condensations of **5** with different imines.^[13c,d] In this hypothesis, the stereochemistry of the two (*S,S*)-lactone units fixed the *R* configuration of the two new C_α/C_{α'} stereocenters of the products. Therefore, even if four new stereocenters formed, only three diastereoisomers can form.^[17] Nevertheless, only *duals* **9** (the major diastereoisomer) and **9'** have been isolated. To explain this behavior, we have hypothesized that a first condensation of **8** with **4** formed complex **A**, driving the (*R*)-C_α and (*S*)-C_β configuration (Scheme 4). Then, after *N*-indium-imine derivative elimination from **A**, a second molecule of silylketene acetal **8** was coordinated. Two diastereoisomeric intermediates, differing from the imine geometry, can be formed. The *Z*-complex **B** (black), presenting the Ar_{ax} group in the less hindered *pseudo*-axial position, can evolve to the major *dual* **9**. The minor stereoisomer **9'** formed *via* intermediate *E*-complex **B'** (red), in which the Ar_{eq} group is flipped into the more hindered *pseudo*-equatorial position. Our stereochemical result is in accord with the “double stereodifferentiation” concept.^[18] Actually, as demonstrated in Scheme 2, the second condensation forming complex **B** occurs between **8** and the intermediate imine **10**, bearing the (*S,S*)-lactone scaffold.



Scheme 4. Mechanism of the Mannich-like condensation.

The formation of the (RR,RR) -dual diastereoisomer, *via* the boat-conformed complex A' (Scheme 5), could also be expected, but this compound did not form, most likely because the steric crowding in A' prevents the first Mannich-like condensation.



Scheme 5. Stereochemical forbidden (RR,RR) -dual diastereoisomer.

The absolute configuration of diastereoisomers **9** was unequivocally assigned by X-ray crystallography of the major diastereoisomers **9e** (Figure 1) and **9a** (Figure S1 in the supporting Information).

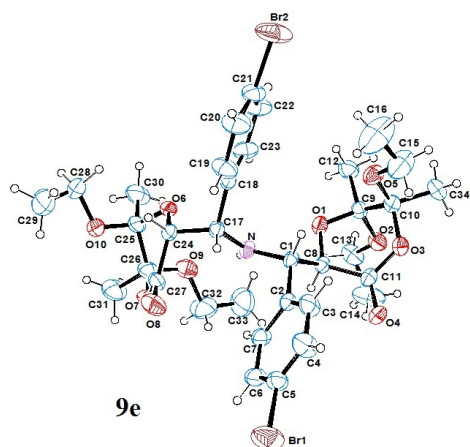
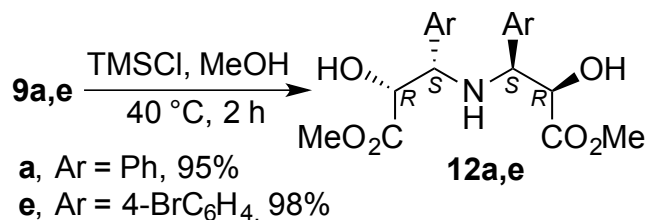


Figure 1. ORTEP^[19] views of **9e**, showing the arbitrary atom-labeling scheme. Thermal ellipsoids are at the 40% probability level.

Finally, with the aim to obtain the *dual* α -hydroxy- β -amino esters **12**, compounds **9a,e** were selected and a methanolysis (TMSCl/MeOH) was performed affording *duals* amino acids **12a,e** in a quasi-quantitative yield (Scheme 6).



Scheme 6. Preparation of *dual* α -hydroxy- β -amino esters **12a,e**.

Conclusion

In summary, we have described the straightforward preparation of *dual* α -hydroxy- β -amino acid derivatives **9/9'**, *via* imine intermediate **10**, by a highly stereoselective Mannich-like condensation between the silylketene acetal **8** derived from the enantiopure (5*S*,6*S*)-5,6-diethoxy-5,6-dimethyl-1,4-

dioxan-2-one and hydroarylamides **4**. By tuning the stoichiometry of the reagents, is it possible to obtain the dual compounds **9/9'** or the imine intermediate **10**, a valuable synthon for further Mannich like condensation reactions.

A mechanism hypothesis, which gives a rationale for the high diastereoselectivity of this procedure, integrates the description of the synthetic protocol proposed in this paper. Compounds **9** can be easily transformed into the corresponding β,β' -diaryl *dual* derivatives **2c**, a very attractive class of amino acids for the synthesis of non-conventional peptidomimetics.

Experimental Section

Mannick-like condensation (*Method B*). Synthesis of *duals* **9**, **9'** and **10**.

Anhydrous MeCN solutions (1 mol L⁻¹) of the reagents **4**, **8** and InCl₃ have been used. In a flame-dried round flask, the InCl₃ solution (4 mL, 0.88 g, 4 mmol) was added to the hydroarylamide **4** solution (2 mL, 2 mmol), at 25 °C and under nitrogen. The resulting mixture was stirred at -30 °C until some solid crystallized (1 h). Then, the (*S,S*)-ketene acetal **8** solution (6 mL, 2.0 g, 6 mmol) was added and the mixture was stirred for further 10 min. Finally, the reaction was quenched by aqueous saturated solution of NaHCO₃ (4 mL) and extracted with AcOEt (3×20mL). The collected organic phases were washed with brine (2×10 mL), dried over Na₂SO₄ and the solvent evaporated under vacuum (RV). The resulting crude was purified by FCC (AcOEt/hexane/TEA, from 10/1/0.01 to 3/1/0.01). Starting hydroarylamide **4**, yield and physical, spectroscopic, and analytical data of *duals* **9a–e** and **9a'–e'**, and of imines **10a–e** are as follows.

(3*R*,3'*R*,5*S*,5'*S*,6*S*,6'*S*)-3,3'-[(1*S*,1'*S*)-azanediylbis(phenylmethylene)]bis(5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one) (9a). Hydrobenzamide (**4a**, 596 mg). **9a** (794 mg, 63%); white solid, mp 130–131 °C; $[\alpha]_D^{20} = +195$ (*c* 1.0, CHCl₃); ee > 99% [HPLC: column KROMASIL 5-AK; 25 °C; *i*-PrOH/hexane (1:10); flow 0.8 mL/min, *t_R* = 7.07 (**9a**) and 7.54 (**9a'**)]. ¹H NMR (300 MHz, CDCl₃) (S-31) δ 7.31–7.29

(m, 6H), 7.21–7.18 (m, 4H), 4.13 (d, 2H, $J = 5.8$ Hz), 3.93 (d, 2H, $J = 5.8$ Hz), 3.66 (q, 4H, $J = 7.0$ Hz), 3.53–3.47 (m, 2H), 3.39–3.34 (m, 2H), 1.50 (s, 6H), 1.47 (s, 6H), 1.09 (t, 6H, $J = 7.0$ Hz), 1.02 (t, 6H, $J = 7.0$ Hz), (NH proton not visible); ^{13}C NMR (75 MHz, CDCl_3) (S-32) δ 167.4 (2C), 138.3 (2C), 128.6 (4C), 128.0 (4C), 127.6 (2C), 104.7 (2C), 98.1 (2C), 75.7 (2C), 61.1 (2C), 58.1 (2C), 57.0 (2C), 18.9 (2C), 17.7 (2C), 15.4 (2C), 15.1 (2C). Anal. Calcd. for $\text{C}_{34}\text{H}_{47}\text{NO}_{10}$: C, 64.85; H, 7.52; N, 2.22. Found: C, 64.61; H, 7.33; N, 2.39.

(3*R*,3'*R*,5*S*,5'*S*,6*S*,6'*S*)-3,3'-[(1*R*,1'*S*)-azanediylbis(phenylmethylene)]bis(5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one) (9a'). 64 mg (5%); white wax; $[\alpha]_{\text{D}}^{20} = +120$ (c 0.96, CHCl_3). ^1H NMR (300 MHz, CDCl_3) (S-34) δ 7.18 (s, 10H), 4.33 (d, 2H, $J = 4.5$ Hz), 4.29 (d, 2H, $J = 4.5$ Hz), 3.56 (q, 4H, $J = 6.0$ Hz), 3.51–3.28 (m, 4H), 1.44 (s, 6H), 1.38 (s, 6H), 1.11 (t, 6H, $J = 4.5$ Hz), 1.34 (t, 6H, $J = 4.5$ Hz), (NH proton not visible); ^{13}C NMR (75 MHz, CDCl_3) (S-35) δ 169.9 (2C), 139.8 (2C), 127.8 (4C), 127.3 (4C), 126.6 (2C), 104.8 (2C), 97.8 (2C), 74.9 (2C), 62.3 (2C), 57.9 (2C), 56.9 (2C), 19.1 (2C), 18.0 (2C), 15.8 (2C), 15.4 (2C). MS (ESI) calcd. for $\text{C}_{34}\text{H}_{47}\text{NO}_{10}$ $[\text{M} + 1]^+$: m/z 630.33; found 630.3 $[\text{M} + 1]^+$, 652.2 $[\text{M} + 23]^+$. Anal. Calcd. for $\text{C}_{34}\text{H}_{47}\text{NO}_{10}$: C, 64.85; H, 7.52; N, 2.22. Found: C, 64.59; H, 7.28; N, 2.44.

(3*R*,5*S*,6*S*)-3-[(*S*)-(benzylideneamino)(phenyl)methyl]-5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one (10a). 148 mg (18%); white wax; $[\alpha]_{\text{D}}^{20} = +47$ (c 1.0, THF). *E* and *Z* mixture: ^1H NMR (300 MHz, CDCl_3) (S-36) δ 8.36 and 8.31 (s, 1H), 7.84–7.81 (m, 2H), 7.55 (d, 2H, $J = 7.1$ Hz), 7.47–7.30 (m, 6H), 5.10 and 5.00 (d, 1H, $J = 4.1$ and 4.5 Hz), 4.61 and 4.57 (d, 1H, $J = 4.5$ and 4.1 Hz), 3.74–3.61 (m, 2H), 3.58–3.42 (m, 1H), 3.38–3.31 (m, 1H), 1.52 and 1.51 (s, 3H), 1.43 (s, 3H), 1.17–1.09 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) (S-37) δ 168.0, 163.3 and 162.2, 139.6, 136.2, 130.8, 128.6 (2C), 128.3 (2C), 128.2 (2C), 128.1 (2C), 127.5, 105.7, 98.5, 74.7, 74.5, 58.6 and 58.4, 57.0, 19.6, 17.7, 15.5, 15.0. MS (ESI) calcd. for $\text{C}_{24}\text{H}_{29}\text{NO}_5$ $[\text{M} + 1]^+$: m/z 412.21; found MS (ESI) m/z 412.2 $[\text{M} + 1]^+$, 434.2 $[\text{M} + 23]^+$. Anal. Calcd. for $\text{C}_{24}\text{H}_{29}\text{NO}_5$: C, 70.05; H, 7.10; N, 3.40. Found: C, 70.28; H, 7.39; N, 3.12.

Enantiomeric *duals* **ent-9a**, **ent-9a'** and **ent-10a** were prepared using the (*R,R*)-TES-ketene acetal **11**.

ent-9a: $[\alpha]_{\text{D}}^{20} = -196.5$ (*c* 1.1, CHCl₃). ¹H NMR matches that of **9a**. Anal. Calcd. for C₃₄H₄₇NO₁₀: C, 64.85; H, 7.52; N, 2.22. Found: C, 64.62; H, 7.33; N, 2.47.

ent-9a': $[\alpha]_{\text{D}}^{20} = -124$ (*c* 1.0, CHCl₃). ¹H NMR matches that of **9a'**. Anal. Calcd. for C₃₄H₄₇NO₁₀: C, 64.85; H, 7.52; N, 2.22. Found: C, 64.74; H, 7.38; N, 2.38.

ent-10a: $[\alpha]_{\text{D}}^{20} = -48$ (*c* 1.0, THF). ¹H NMR matches that of **10a**. Anal. Calcd. for C₂₄H₂₉NO₅: C, 70.05; H, 7.10; N, 3.40. Found: C, 70.31; H, 7.41; N, 3.22.

(3*R*,3'*R*,5*S*,5'*S*,6*S*,6'*S*)-3,3'-[(1*S*,1'*S*)-azanediylbis(*p*-tolylmethylene)]bis(5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one) (9b). Hydrotoluamide (**4b**, 680 mg). **9b** (672 mg, 51%); wax; $[\alpha]_{\text{D}}^{20} = +214$ (*c* 1.0, CHCl₃). ¹H NMR (300 MHz, CDCl₃) (S-38) δ 7.11 (d, 4H, *J* = 8.2 Hz), 7.07 (d, 4H, *J* = 8.2 Hz), 4.10 (d, 2H, *J* = 5.8 Hz), 3.87 (d, 2H, *J* = 5.5 Hz), 3.64 (q, 4H, *J* = 7.0 Hz), 3.53–3.36 (m, 4H), 2.33 (s, 6H), 1.49 (s, 6H), 1.46 (s, 6H), 1.08 (t, 6H, *J* = 7.0 Hz), 1.00 (t, 6H, *J* = 7.0 Hz) (NH proton not visible); ¹³C NMR (75 MHz, CDCl₃) (S-39) δ 167.5 (2C), 136.9 (2C), 135.3 (2C), 128.8 (4C), 128.5 (4C), 104.7 (2C), 98.1 (2C), 75.8 (2C), 60.8 (2C), 58.1 (2C), 57.0 (2C), 21.2 (2C), 19.0 (2C), 17.7 (2C), 15.3 (2C), 15.1 (2C). Anal. Calcd. for C₃₆H₅₁NO₁₀: C, 65.73; H, 7.81; N, 2.13. Found: C, 66.02; H, 8.05; N, 1.98.

(3*R*,3'*R*,5*S*,5'*S*,6*S*,6'*S*)-3,3'-[(1*S*,1'*R*)-azanediylbis(*p*-tolylmethylene)]bis(5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one) (9'b). 106 mg (8%); white wax; $[\alpha]_{\text{D}}^{20} = +123$ (*c* 1.0, CHCl₃). ¹H NMR (300 MHz, CDCl₃) (S-41) δ 7.31 (d, 4H, *J* = 7.9 Hz), 7.15 (d, 4H, *J* = 7.9 Hz), 4.51 (d, 2H, *J* = 1.9 Hz), 4.33 (d, 2H, *J* = 2.5 Hz), 3.81–3.66 (m, 4H), 3.52–3.44 (m, 2H), 3.35–3.29 (m, 2H), 2.36 (s, 6H), 1.53 (s, 6H), 1.41 (s, 6H), 1.20 (t, 6H, *J* = 7.0 Hz), 1.13 (t, 6H, *J* = 7.0 Hz) (NH proton not visible). Anal. Calcd. for C₃₆H₅₁NO₁₀: C, 65.73; H, 7.81; N, 2.13. Found: C, 65.84; H, 7.79; N, 2.02.

(3*R*,5*S*,6*S*)-5,6-diethoxy-5,6-dimethyl-3-{(*S*)-[(4-methylbenzylidene)amino](*p*-tolyl)methyl}-1,4-dioxan-2-one (10b). 212 mg (24%); wax; $[\alpha]_{\text{D}}^{20} = +43$ (*c* 1.2, CHCl₃). *E* and *Z* mixture: ¹H NMR (300 MHz, CDCl₃) (S-42) δ 8.31 and 8.28 (s, 1H), 7.71 (d, 2H, *J* = 7.8 Hz), 7.42 (d, 2H, *J* = 7.8 Hz), 7.22–7.13 (m, 4H), 5.04 and 4.98 (d, 1H, *J* = 4.1 and 4.2 Hz), 4.61 and 4.55 (d, 1H, *J* = 4.2 and 4.1 Hz),

3.80–3.56 (m, 2H), 3.54–3.44 (m, 1H), 3.44–3.29 (m, 1H), 2.39 (s, 3H), 2.37 (s, 3H), 1.52 (s, 3H), 1.42 and 1.41 (s, 3H), 1.17–1.13 (m, 6H). Anal. Calcd. for C₂₆H₃₃NO₅: C, 71.05; H, 7.57; N, 3.19. Found: C, 70.81; H, 7.36; N, 3.38.

(3*R*,3'*R*,5*S*,5'*S*,6*S*,6'*S*)-3,3'-{(1*S*,1'*S*)-azanediylbis[(4-methoxyphenyl)methylene]}bis(5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one) (9c). Hydro(4-methoxy)benzamide (**4c**, 776 mg). **9c** (648 mg, 47%); wax; [α]_D²⁰ = +168 (*c* 1.3, CHCl₃). ¹H NMR (300 MHz, CDCl₃) (S-43) δ 7.11 (d, 4H, *J* = 8.5 Hz), 6.84 (d, 4H, *J* = 8.7 Hz), 4.09 (d, 2H, *J* = 6.0 Hz), 3.86 (d, 2H, *J* = 6.0 Hz), 3.81 (s, 6H), 3.66 (d, 2H, *J* = 14.1 Hz), 3.64 (d, 2H, *J* = 14.1 Hz), 3.55–3.33 (m, 4H), 1.49 (s, 6H), 1.46 (s, 6H), 1.09 (t, 6H, *J* = 7.3 Hz), 1.02 (t, 6H, *J* = 7.0 Hz) (NH proton not visible); ¹³C NMR (75 MHz, CDCl₃) (S-44) δ 167.4 (2C), 158.9 (2C), 130.3 (2C), 129.5 (4C), 113.3 (4C), 104.6 (2C), 97.9 (2C), 75.6 (2C), 60.3 (2C), 57.9 (2C), 56.8 (2C), 54.9 (2C), 18.7 (2C), 17.5 (2C), 15.2 (2C), 14.9 (2C). Anal. Calcd. for C₃₆H₅₁NO₁₂: C, 62.68; H, 7.45; N, 2.03. Found: C, 62.95; H, 7.74; N, 1.82.

(3*R*,3'*R*,5*S*,5'*S*,6*S*,6'*S*)-3,3'-{(1*S*,1'*R*)-azanediylbis[(4-methoxyphenyl)methylene]}bis(5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one) (9c'). 82 mg (6%); white wax; [α]_D²⁰ = +78 (*c* 1.4, CHCl₃). ¹H NMR (300 MHz, CDCl₃) (S-46) δ 7.35 (d, 4H, *J* = 8.7 Hz), 6.89 (d, 4H, *J* = 8.7 Hz), 4.53 (d, 2H, *J* = 2.8 Hz), 4.40 (d, 2H, *J* = 2.8 Hz), 3.82 (s, 6H), 3.73–3.62 (m, 4H), 3.56–3.49 (m, 2H), 3.45–3.36 (m, 2H), 1.52 (s, 6H), 1.42 (s, 6H), 1.18–1.14 (m, 12H) (NH proton not visible); ¹³C NMR (75 MHz, CDCl₃) (S-47) δ 169.0 (2C), 159.0 (2C), 133.3 (2C), 128.4 (4C), 113.6 (4C), 105.3 (2C), 98.1 (2C), 74.5 (2C), 58.4 (2C), 57.3 (2C), 56.5 (2C), 55.2 (2C), 18.5 (2C), 17.6 (2C), 15.2 (2C), 15.0 (2C). Anal. Calcd. for C₃₆H₅₁NO₁₂: C, 62.68; H, 7.45; N, 2.03. Found: C, 62.97; H, 7.79; N, 1.83.

(3*R*,5*S*,6*S*)-5,6-diethoxy-3-{(*S*)-[(4-methoxybenzylidene)amino](4-methoxyphenyl)methyl}-5,6-dimethyl-1,4-dioxan-2-one (10c). 236 mg (25%); wax; [α]_D²⁰ = +15.8 (*c* 1.0, CHCl₃). *E* and *Z* mixture: ¹H NMR (300 MHz, CDCl₃) (S-49) δ 8.25 and 8.22 (s, 1H), 7.74 (d, 2H, *J* = 8.7 Hz), 7.45 (d, 2H, *J* = 8.6 Hz), 6.91–6.88 (m, 4H), 5.00 and 4.95 (d, 1H, *J* = 4.2 and 4.5 Hz), 4.57 and 4.49 (d, 1H, *J* = 4.5 and

4.2 Hz), 3.82 (s, 3H), 3.80 and 3.78 (s, 3H), 3.74–3.59 (m, 2H), 3.52–3.44 (m, 1H), 3.43–3.27 (m, 1H), 1.50 (s, 3H), 1.41 (s, 3H), 1.16–1.10 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) (S-50) δ 168.0 and 167.6, 161.9 and 161.1, 161.7, 158.9, 132.1, 130.1 (2C), 129.4, 129.2 (2C), 113.7 (2C), 113.6 (2C), 105.5, 98.5, 74.8, 73.8, 58.5, 56.9, 55.3, 55.2, 19.7, 17.7, 15.5, 15.0. Anal. Calcd. for $\text{C}_{26}\text{H}_{33}\text{NO}_7$: C, 66.22; H, 7.05; N, 2.97. Found: C, 66.47; H, 7.23; N, 2.74.

(3*R*,3'*R*,5*S*,5'*S*,6*S*,6'*S*)-3,3'-{(1*S*,1'*S*)-azanediylbis[(4-fluorophenyl)methylene]}bis(5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one) (9d). Hydro(4-fluoro)benzamide (**4d**, 708 mg). **9d** (572 mg, 43%); white wax; $[\alpha]_{\text{D}}^{20} = +198$ ($c = 1.4$ CHCl_3). ^1H NMR (300 MHz, CDCl_3) (S-52) δ 7.20–7.15 (m, 4H), 7.04–6.99 (m, 4H), 4.09 (d, 2H, $J = 5.7$ Hz), 3.90 (d, 2H, $J = 5.7$ Hz), 3.69 (q, 4H, $J = 7.0$ Hz), 3.58 (bs, 1H), 3.60–3.48 (m, 2H), 3.42–3.32 (m, 2H), 1.52 (s, 6H), 1.48 (s, 6H), 1.13–1.03 (m, 12H); ^{13}C NMR (75 MHz, CDCl_3) (S-53) δ 167.3 (2C), 162.4 (d, 2C, $J = 245.4$ Hz), 133.9 (2C), 130.1 (d, 4C, $J = 8.1$ Hz), 115.0 (d, 4C, $J = 21.3$ Hz), 104.9 (2C), 98.1 (2C), 75.5 (2C), 60.4 (2C), 58.2 (2C), 57.1 (2C), 18.8 (2C), 17.6 (2C), 15.3 (2C), 15.0 (2C). Anal. Calcd. for $\text{C}_{34}\text{H}_{45}\text{F}_2\text{NO}_{10}$: C, 61.34; H, 6.81; N, 2.10. Found: C, 61.43; H, 6.90; N, 2.02.

(3*R*,3'*R*,5*S*,5'*S*,6*S*,6'*S*)-3,3'-{(1*S*,1'*R*)-azanediylbis[(4-fluorophenyl)methylene]}bis(5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one) (9d'). 94 mg (7%); white wax; $[\alpha]_{\text{D}}^{20} = +48$ ($c = 1.0$, CHCl_3). ^1H NMR (300 MHz, CDCl_3) (S-55) δ 7.42–7.38 (m, 4H), 7.08–7.03 (m, 4H), 5.12 (d, 2H, $J = 4.4$ Hz), 4.27 (d, 2H, $J = 4.5$ Hz), 4.03 (bs, 1H), 3.83–3.70 (m, 4H), 3.64–3.52 (m, 4H), 1.56 (s, 6H), 1.45 (s, 6H), 1.26 (t, 6H, $J = 7.1$ Hz), 1.19 (t, 6H, $J = 7.1$ Hz); ^{13}C NMR (75 MHz, CDCl_3) (S-56) δ 166.9 (2C), 162.4 (d, 2C, $J = 246.0$ Hz), 134.0 (2C), 128.5 (d, 4C, $J = 7.9$ Hz), 114.9 (d, 4C, $J = 21.4$ Hz), 105.1 (2C), 98.1 (2C), 75.7 (2C), 73.9 (2C), 58.9 (2C), 57.5 (2C), 18.6 (2C), 17.5 (2C), 15.1 (4C). Anal. Calcd. for $\text{C}_{34}\text{H}_{45}\text{F}_2\text{NO}_{10}$: C, 61.34; H, 6.81; N, 2.10. Found: C, 61.47; H, 6.96; N, 2.00.

(3*R*,5*S*,6*S*)-5,6-diethoxy-3-[(*S*)-[(4-fluorobenzylidene)amino](4-fluorophenyl)methyl]-5,6-

dimethyl-1,4-dioxan-2-one (10d). 448 mg (50%); wax; $[\alpha]_{\text{D}}^{20} = +37$ (*c* 1.4, CHCl₃). *E* and *Z* mixture:

¹H NMR (300 MHz, CDCl₃) (S-58) δ 8.31 and 8.26 (s, 1H), 7.84–7.79 (m, 2H), 7.54–7.49 (m, 2H), 7.12–7.03 (m, 4H), 5.05 and 4.98 (d, 1H, *J* = 4.2 and 4.8 Hz), 4.54 and 4.47 (d, 1H, *J* = 4.8 and 4.2 Hz), 3.70–3.58 (m, 2H), 3.55–3.45 (m, 1H), 3.36–3.26 (m, 1H), 1.51 (s, 3H), 1.42 (s, 3H), 1.17–1.07 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) (S-59) δ 167.9, 164.5 (d, *J* = 249.0 Hz), 162.2 (d, *J* = 244.0 Hz), 161.8, 135.4 (d, *J* = 2.8 Hz), 132.4 (d, *J* = 2.5 Hz), 130.6 (d, 2C, *J* = 8.7 Hz), 129.7 (d, 2C, *J* = 7.7 Hz), 115.5 (d, 2C, *J* = 22.1 Hz), 115.1 (d, 2C, *J* = 21.0 Hz), 105.7, 98.5, 74.7, 73.7, 58.5, 57.0, 19.3, 17.7, 15.5, 15.0. Anal. Calcd. for C₂₄H₂₇F₂NO₅: C, 64.42; H, 6.08; N, 3.13. Found: C, 64.71; H, 6.29; N, 3.00.

Enantiomeric *duals* **ent-9d** and **ent-10d** were prepared using the silyl derivative (*R,R*)-TES-ketene acetal **11**.

ent-9d: $[\alpha]_{\text{D}}^{20} = -194$ (*c* 1.4, CHCl₃). ¹H NMR matches that of **9d**. Anal. Calcd. for C₃₄H₄₅F₂NO₁₀: C, 61.34; H, 6.81; N, 2.10. Found: C, 61.53; H, 7.06; N, 1.95.

ent-10d: $[\alpha]_{\text{D}}^{20} = -34$ (*c* 1.6, CHCl₃). ¹H NMR matches that of **10d**. Anal. Calcd. for C₂₄H₂₇F₂NO₅: C, 64.42; H, 6.08; N, 3.13. Found: C, 64.65; H, 6.33; N, 2.92.

(3*R*,3'*R*,5*S*,5'*S*,6*S*,6'*S*)-3,3'-[(1*S*,1'*S*)-azanediylbis[(4-bromophenyl)methylene]]bis(5,6-diethoxy-

5,6-dimethyl-1,4-dioxan-2-one) (9e). Hydro(4-bromo)benzamide **4e** (1.07 g). **9e** (0.94 g, 60%); white

wax; $[\alpha]_{\text{D}}^{20} = +224$ (*c* = 1.1, CHCl₃). ¹H NMR (300 MHz, CDCl₃) (S-61) δ 7.44 (d, 4H, *J* = 8.4 Hz), 7.07 (d, 4H, *J* = 8.3 Hz), 4.09 (d, 2H, *J* = 5.2 Hz), 3.84 (d, 2H, *J* = 5.2 Hz), 3.70–3.62 (m, 5H), 3.57–3.47 (m, 2H), 3.42–3.32 (m, 2H), 1.50 (s, 6H), 1.46 (s, 6H), 1.11 (t, 6H, *J* = 7.0 Hz), 1.03 (t, 6H, *J* = 7.0 Hz); ¹³C NMR (75 MHz, CDCl₃) (S-62) δ 167.2 (2C), 137.2 (2C), 131.3 (4C), 130.3 (4C), 121.7 (2C), 104.9 (2C), 98.2 (2C), 75.2 (2C), 60.6 (2C), 58.2 (2C), 57.1 (2C), 18.8 (2C), 17.6 (2C), 15.3 (2C), 15.0 (2C). Anal. Calcd. for C₃₄H₄₅Br₂NO₁₀: C, 51.85; H, 5.76; N, 1.78. Found: C, 52.03; H, 5.92; N, 1.61.

(3*R*,3'*R*,5*S*,5'*S*,6*S*,6'*S*)-3,3'-{(1*S*,1'*R*)-azanediylbis[(4-bromophenyl)methylene]}bis(5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one) (9e'). 126 mg (8%); white wax; $[\alpha]_{\text{D}}^{20} = +123$ ($c = 1.1$ CHCl₃). ¹H NMR (300 MHz, CDCl₃) (S-64) δ 7.47 (d, 4H, $J = 8.4$ Hz), 7.30 (d, 4H, $J = 8.5$ Hz), 4.49 (d, 2H, $J = 2.3$ Hz), 4.28 (d, 2H, $J = 2.3$ Hz), 3.80–3.66 (m, 4H), 3.54–3.43 (m, 2H), 3.33–3.23 (m, 2H), 2.03 (bs, 1H), 1.53 (s, 6H), 1.39 (s, 6H), 1.20 (t, 6H, $J = 7.0$ Hz), 1.13 (t, 6H, $J = 7.1$ Hz). Anal. Calcd. for C₃₄H₄₅Br₂NO₁₀: C, 51.85; H, 5.76; N, 1.78. Found: C, 52.07; H, 5.94; N, 1.59.

(3*R*,5*S*,6*S*)-3-{(S)-[(4-bromobenzylidene)amino](4-bromophenyl)methyl}-5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one (10e). 296 mg (26%); wax; $[\alpha]_{\text{D}}^{20} = +23$ ($c = 1.2$, CHCl₃). *E* and *Z* mixture: ¹H NMR (300 MHz, CDCl₃) (S-65) δ 8.27 and 8.24 (s, 1H), 7.68 (d, 2H, $J = 8.4$ Hz), 7.57–7.38 (m, 6H), 5.01 and 4.94 (d, 1H, $J = 4.0$ and 4.7 Hz), 4.51 and 4.46 (d, 1H, $J = 4.6$ and 4.1 Hz), 3.66–3.26 (m, 4H), 1.49 (s, 3H), 1.40 (s, 3H), 1.16–1.06 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) (S-66) δ 168.3 and 167.7, 162.2 and 161.3, 138.5, 134.9, 131.6 (2C), 131.3 (2C), 130.0 (2C), 129.9 (2C), 125.4, 121.5, 105.8 and 105.2, 98.5 and 98.1, 74.7 and 74.4, 73.8, 58.5, 57.3 and 57.0, 19.3, 17.7, 15.5, 15.0. Anal. Calcd. for C₂₄H₂₇Br₂NO₅: C, 50.64; H, 4.78; N, 2.46. Found: C, 50.40; H, 4.51; N, 2.68.

Synthesis of 9d from imine 10d.

Anhydrous MeCN solutions (1 mol L⁻¹) of **10d**, **8** and InCl₃ have been used. In a flame-dried round flask, the InCl₃ solution (0.5 mL, 110 mg, 0.5 mmol) was added to the imine **10d** solution (0.5 mL, 224 mg, 0.5 mmol), at 25 °C and under nitrogen. The resulting mixture was stirred at -30 °C until some solid crystallized (1 h). Then, the (*S,S*)-ketene acetal **8** solution (0.75 mL, 249 mg, 0.75 mmol) was added and the mixture was stirred for further 10 min. Finally, the reaction was quenched by aqueous saturated solution of NaHCO₃ (1 mL) and extracted with AcOEt (3×5 mL). The collected organic phases were washed with brine (2×5 mL), dried over Na₂SO₄ and the solvent evaporated under vacuum (RV). The resulting crude was purified by FCC (AcOEt/hexane/TEA, from 10/1/0.01 to 3/1/0.01) and

9d was isolated (156 mg, 47%). The physical, analytical and spectroscopic data match those of **9d** prepared by reaction of **4d** with **8**.

Synthesis of *dual* α -hydroxy- β -amino esters **12a,e**.

A solution of trimethylsilyl chloride (164 mg, 1.5 mmol) and compound **9** (1 mmol) in MeOH (4 mL) was stirred at 40 °C for 2 h. After evaporation of the solvent under vacuum, the residue was diluted with saturated aqueous NaHCO₃ solution (5 mL) and extracted with dichloromethane (2×10 mL). The collected organic phases were dried over Na₂SO₄, filtered and concentrated under vacuum affording pure compound **12**.

(2*R*,2'*R*,3*S*,3'*S*)-dimethyl 3,3'-azanediylbis(2-hydroxy-3-phenylpropanoate) (12a). *Dual 9a* (630 mg). **12a** (366 mg, 98%); white wax; $[\alpha]_{\text{D}}^{20} = +92$ (*c* 0.9 CHCl₃). ¹H NMR (300 MHz, CDCl₃) (S-67) δ 7.35–7.31 (m, 6H), 7.22–7.20 (m, 4H), 4.20 (d, 2H, *J* = 4.9 Hz), 3.65 (d, 2H, *J* = 4.9 Hz), 3.60 (s, 6H), 3.44 (bs, 3H); ¹³C NMR (75 MHz, CDCl₃) (S-68) δ 173.6 (2C), 138.8 (2C), 128.4 (4C), 128.1 (4C), 128.0 (2C), 75.2 (2C), 61.8 (2C), 52.2 (2C); IR (KBr) ν_{max} 3412, 3320, 1755, 1206, 1149, 744 cm⁻¹. MS (ESI) *m/z* 374.1 [M + 1]⁺, 396.1 [M + 23]⁺. Anal. Calcd. for C₂₀H₂₃NO₆: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.57; H, 6.51; N, 3.48.

(2*R*,2'*R*,3*S*,3'*S*)-dimethyl 3,3'-azanediylbis(3-(4-bromophenyl)-2-hydroxypropanoate) (12e). *Dual 9e* (788 mg). **12e** (526 mg, 99%); white wax; $[\alpha]_{\text{D}}^{20} = +140$ (*c* 1.1, CHCl₃). ¹H NMR (300 MHz, CDCl₃) (S-69) δ 7.48 (d, 4H, *J* = 8.3 Hz), 7.09 (d, 4H, *J* = 8.4 Hz), 4.14 (d, 2H, *J* = 4.7 Hz), 3.65 (s, 6H), 3.56 (d, 2H, *J* = 4.7 Hz), 3.09 (bs, 3H); ¹³C NMR (75 MHz, CDCl₃) (S-70) δ 172.7 (2C), 137.1 (2C), 131.1 (4C), 129.2 (4C), 121.5 (2C), 74.2 (2C), 60.6 (2C), 51.9 (2C). Anal. Calcd. for C₂₀H₂₁Br₂NO₆: C, 45.22; H, 3.98; N, 2.64. Found: C, 44.94; H, 3.68; N, 2.93.

Acknowledgments. We are grateful for funding to MIUR (2015 PRIN project Prot. 20157WW5EH) and CNR (Italy).

Conflict of interest

The authors declare no conflict of interest.

Keywords

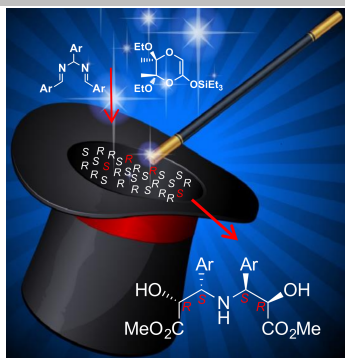
- a) Diastereoselectivity
- b) Enols
- c) Mannich-like reaction
- d) Hydroarylamides
- e) Dual α -hydroxy- α -amino acids

Supporting Information Available. Synthesis of compounds **4a–e**, **8,11**. Copies of ^1H and ^{13}C NMR spectra of synthesized compounds. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers: CCDC-1533981 (**9a**) and CCDC-1533983 (**9e**). These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Key Topic

Dual amino acids

Dual α,α' -Dihydroxy- β -amino acids were prepared in very good yields and with different aryl substitution patterns. Taking advantage of the “double stereodifferentiation” concept, a highly stereoselective reaction was performed: of the 16 possible isomers, only two diastereoisomers (*d.r.* up to 93:7) formed.



Ilijir Pecnikaj, Francesca Foschi, Maria Luisa Gelmi, Carlo Castellano, Fiorella Meneghetti, and Michele Penso*

Page No. – Page No.

Stereoselective Synthesis of α,α' -Dihydroxy- β,β' -diaryl- β -amino Acids by Mannich-like Condensation of Hydroarylamides

References and Notes

- [1] a) J. W. Checco, S. H. Gellman, *Curr. Opin. Struct. Biol.* **2016**, *39*, 96–105; b) C. Cabrele, T. A. Martinek, O. Reiser, Ł. Berlicki, *J. Med. Chem.* **2014**, *57*, 9718–9739; c) C. T. Walsh, R. V. O'Brien, C. Khosla, *Angew. Chem. Int. Edit.* **2013**, *52*, 7098–7124; d) G. H. Hur, C. R. Vickery, M. D. Burkart, *Nat. Prod. Rep.* **2012**, *29*, 1074–1098; e) W.S. Horne, *Expert Opin. Drug Discov.* **2011**, *6*, 1247; f) E. Juaristi, V. A. Soloshonok, *Enantioselective Synthesis of β -Amino Acids*, 2nd ed, John Wiley&Sons, Inc, NJ, **2005**; g) D. G. I. Kingston, P. J. Jagtap, H. Yuan, L. Samala, *Progress in the Chemistry of Organic Natural Products*, , Springer-Verlag, Wien & New York, **2002**, *84*, 53–225.
- [2] a) R. Bucci, A. Contini, F. Clerici, S. Pellegrino, M. L. Gelmi, *Org. Chem. Front.* **2019**, *6*, 972–982; b) R. Bucci, A. Contini, F. Clerici, E. M. Beccalli, F. Formaggio, I. Maffucci, S. Pellegrino, M. L. Gelmi, *Frontiers in chemistry* **2019**, *7*, 192; c) R. Bucci, A. Bonetti, F. Clerici, A. Contini, D. Nava, S. Pellegrino, D. Tessaro, M. L. Gelmi, *Chem. Eur. J.* **2017**, *23*, 10822–10831; d) W. Lee, S. Kwon, P. Kang, I. A. Guzei, S. H. Choi, *Org. Biomol. Chem.* **2014**, *12*, 2641–2644; e) L. K. A. Pilsl, O. Reiser, *Amino Acids* **2011**, *41*, 709; g) D. Seebach, J. Gardiner, *Acc. Chem. Res.* **2008**, *41*, 1366–1375; g) S. Hecht, I. Huc, *Foldamers: Structure, Properties, and Applications*; Wiley-VCH, Germany, **2007**; h) D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes, J. S. Moore, *Chem. Rev.* **2001**, *101*, 3893–4011; i) R. P. Cheng, S. H. Gellman, W. F. DeGrado, *Chem. Rev.* **2001**, *101*, 3219–3232; j) S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173–180; m) D. Seebach, J. L. Matthews, *Chem. Comm.* **1997**, 2015–2022.
- [3] a) R. Bucci, P. Das, F. Iannuzzi, M. Feligioni, R. Gandolfi, M. L. Gelmi, M. Reches, S. Pellegrino, *Org. Biomol. Chem.* **2017**, *15*, 6773–6779; b) F. Clerici, E. Erba, M. L. Gelmi, S. Pellegrino, *Tetrahedron Lett.* **2016**, *57*, 5540–5550.
- [4] a) S. C. Deshmukh, P. Talukdar, *J. Org. Chem.* **2014**, *79*, 11215–11225; b) A. Contini, G. Cappelletti, D. Cartelli, G. Fontana, M. L. Gelmi, *Molecular BioSystem*, **2012**, *8*, 3254–3261; c) B. Ke, Y. Qin, F. Zhao, Y. Qu, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4783–4785; d) K. Shimamoto, *Chem. Rec.* **2008**, *8*, 182–199; e) S. Matthijs, H. Budzikiewicz, M. Schafer, B. Wathelet, P. Z. Cornelis, *Naturforsch., C: J. Biosci.* **2008**, *63*, 8–12; f) S. Thoret, F. Gueritte, D. Guenard, J. Dubois, *Org. Lett.* **2006**, *8*, 2301–2304; g) S. Weik, T. Luksch, A. Evers, J. Böttcher, C. A. Sottriffer, A. Hasilik, H.-G. Löffler, G. Klebe, J. Rademann, *Chem. Med. Chem* **2006**, *1*, 445–457; h) A. Battaglia, E. Baldelli, E. Bombardelli, G. Carenzi, G. Fontana, M. L. Gelmi, A. Guerrini, D.

- Pocar, *Tetrahedron* **2005**, *61*, 7727–7745; i) B. K. Hubbard, M. G. Thomas, C. T. Walsh, *Chem. Biol.* **2000**, *7*, 931–942.
- [5] a) S. Hashimoto, Y. Nagamine, JP 2002069491 A 20020308; b) H. Danjo, Y. Kaneko, JP 10140189 A 19980526; c) Y. Yoneyama, JP 09310097 A 19971202; d) M. R. Giles, N. Dixon, WO 2010084351 A1 20100729; e) K. Yokoi, M. Takahashi, JP 11310559 A 1999110; f) R. Baur, C. Gousetis, S. Birnbach, M. Kneip, A. Oftring, EP 411436 A2 19910206.
- [6] Y. Asakawa, Y. Sumita, J. Kita, JP 07325377 A 19951212.
- [7] T. Murakami, M. Nakamura, K. A. Nakamura, JP 2010204243 A 20100916.
- [8] a) H. Hikita, Y. Ayama, Jpn. Kokai Tokkyo Koho (2014), JP 2014088477 A 20140515; b) Y. Sumita, Y. Asakawa, J. Kita, Jpn. Kokai Tokkyo Koho (1995), JP 07284790 A 19951031.
- [9] A. J. O'Lenick, Jr. U.S. (2003), US 6642192 B1 20031104.
- [10] D. L. Parker, C. D. Wilson, G. S. Puritch, D. S. Almond, PCT Int. Appl. (2007), WO 2007031565 A2 20070322.
- [11] P. B. Grascha, M. Battut, U.S. Pat. Appl. Publ. (2010), US 20100040702 A1 20100218.
- [12] R. Crovetto, C. C. Pierce, P. D. Deck, PCT Int. Appl. (2010), WO 2010062461 A1 20100603.
- [13] a) A. Bonetti, E. Beccalli, A. Caselli, F. Clerici, S. Pellegrino, M. L. Gelmi, *Chem. - Eur. J.* **2015**, *21*, 1692–1703; b) A. Bonetti, F. Clerici, F. Foschi, D. Nava, S. Pellegrino, M. Penso, R. Soave, M. L. Gelmi, *Eur. J. Org. Chem.* **2014**, 3203–3209; c) F. Gassa, A. Contini, G. Fontana, S. Pellegrino, M. L. Gelmi, *J. Org. Chem.* **2010**, *75*, 7099–7106; d) M. Penso, F. Foschi, S. Pellegrino, A. Testa, M. L. Gelmi, *J. Org. Chem.* **2012**, *77*, 3454–3461; e) A. Ruffoni, A. Casoni, S. Pellegrino, M. L. Gelmi, R. Soave, F. Clerici, *Tetrahedron* **2012**, *68*, 1951–1962; f) F. Clerici, F. A. Gambini, M. L. Gelmi, D. Nava *Tetrahedron* **2001**, *57*, 6429–6438.
- [14] a) S. Thoret, F. Gueritte, D. Guenard, J. Dubois, *Org. Lett.* **2006**, *8*, 2301–2304; b) S. Torssell, M. Kienle, P. Somfai, *Angew. Chem. Int. Edit.* **2005**, *44*, 3096–3099; c) Y. Zhao, N. Jiang, S. Chen, C. Peng, X. Zhang, Y. Zou, S. Zhang, J. Wang, *Tetrahedron*, **2005**, *61*, 6546–6552; d) J. Chen, L. V. Kuznetsova, I. M. Ungreanu, I. Ojima, In ref. 1f, pp 447–476; e) J. T. Spletstoser, P. T. Flaherty, R. H. Himes, G. I. Georg, *J. Med. Chem.* **2004**, *47*, 6459–6465; f) F. Fringuelli, F. Pizzo, M. Rucci, L. Vaccaro, *J. Org. Chem.* **2003**, *68*, 7041–7045; g) J. E. Semple, T. D. Owens, K. Nguyen, O. E. Levy, *Org. Lett.* **2000**, *2*, 2769–2772.
- [15] a) S. V. Ley, T. D. Sheppard, R. M. Myers, M. S. Chorghade, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1451–1472, and references therein; b) C. F. Carter, I. R. Baxendale, J. B. J. Pavey, S. V. Ley, *Org. Biomol. Chem.* **2010**, *8*, 1588–1595.

- [16] Hydroarylamides **5** were obtained by standard literature methods, inspired by seminal works of M. A. Laurent described in *Annales de Chimie (Cachan, France)*, **1836**, 2, 62 and *Liebigs Ann. Chem.* **1837**, 21, 130.
- [17] The equation $2^{n-1} + 2^{\frac{n-2}{2}}$ was applied (n = new stereocenters).
- [18] “The combined interactions of chiral centers in both intermediate imine and enolate gave an higher stereoselection when a similar stereochemistry is present in both reagents”. F. A. Carey, R. J. Sundberg, in *Advanced Organic Chemistry: (Part B) Reactions and synthesis*, 5th ed, 2007, Springer, p. 111.
- [19] L. J. Farrugia, *J. Appl. Cryst.* **1997**, 30, 565.